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EXPERT REPORT

DAVID A. KESSLER, M.D.

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I. QUALIFICATIONS

1. My name is David A. Kessler, M.D. I received my M.D. degree from Harvard Medical School in 1979 and my J.D. degree from the University of Chicago Law School in 1978.

2. I did my pediatrics training at John Hopkins Hospital.

3. I was appointed in 1990 by President George H.W. Bush as Commissioner of the United States Food and Drug Administration and was confirmed by the United States Senate. I also served in that position under President William Jefferson Clinton until February 1997.

4. I have taught food and drug law at Columbia University Law School, and I have testified many times before the United States Congress on food, drug, and consumer protection issues under federal and state law. Over the last thirty years, I have published numerous articles in legal, medical, and scientific journals on the federal regulation of food, drugs, and medical devices. I have had special training in pharmacoepidemiology at Johns Hopkins Hospital. My resume is included as Appendix A. A list of cases in which I have appeared as a witness in the last five years and documentation of my expert witness fee is attached as Appendix B. A list of my published articles relating to FDA issues, including drugs and devices, is attached as Appendix E.

5. As Commissioner, I had ultimate responsibility for implementing and enforcing the United States Food, Drug, and Cosmetic Act. I was responsible for overseeing five Centers within FDA. They included, among others, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Biologics Evaluation and research. In addition to those duties, I placed high priority on getting promising therapies for serious and life-threatening diseases to patients as quickly as possible. During my tenure as Commissioner, the FDA announced a number of new programs, including: the regulation of the

marketing and sale of tobacco products to children; nutrition labeling for food; user fees for drugs and biologics; preventive controls to improve food safety; measures to strengthen the nation's blood supply; and the MEDWatch program for reporting adverse events and product problems involving both drugs and devices. I created an Office of Criminal Investigation within the Agency. I was directly involved with the regulation of medical devices. Appendix D lists regulations that I signed during my tenure that related to the device approval process. In addition, I established "The Committee for Clinical Review" that reviewed device evaluation and review. I worked closely with FDA's Division of Drug Marketing, Advertising and Communications and was involved in establishing the Center for Devices and Radiological Health's Promotion and Advertising Policy Staff.

6. I am a senior advisor to TPG Capital, a leading global private equity firm, which owns pharmaceutical and biomedical companies. I served on the board of Aptalis Pharma and serve on the boards of Tokai Pharmaceuticals, STOKE Therapeutics, and the medical device and biologics company Immucor, Inc. In these advisory and fiduciary capacities, I have advised companies on the standards and duties of care within the pharmaceutical and medical device industry. I also chaired the compliance committee of Aptalis, and I chair the quality committee of Immucor, which involves ensuring compliance with FDA laws and requirements.

7. The documents provided to me by counsel, or that I accessed independently from various sources, including, but not limited to, FDA's website, are listed in Appendix C to this report. At my request, Appendix C was prepared by counsel. Based on my review of those documents and my training and experience, I have a number of opinions that are detailed below.

8. In this report I use the term "Bard" to mean any of the following entities: Impra, Nitinol Medical Technologies ("NMT"), C.R. Bard, Inc., or Bard Peripheral Vascular.

9. The causes of action in related to this litigation include: negligence, negligent design, negligent manufacture, negligent failure to recall/retrofit, negligent failure to warn, negligence per se, strict products liability - failure to warn, strict products liability - design defect, strict products liability - manufacturing defect, breach of express warranty, breach of implied warranty of merchantability, breach of implied warranty of fitness for a particular purpose, fraudulent concealment, negligent misrepresentation, fraudulent misrepresentation, violations of relevant state laws prohibiting consumer fraud and unfair deceptive trade practices, loss of consortium, wrongful death, survival, and punitive damages.

II. OVERVIEW

10. All manufacturers of medical devices need to ensure the safety of their devices and respond reasonably to evidence of safety concerns.

11. A device manufacturer must assure that the quality of its device does not "fall below, that which it purports or is represented to possess." 21 U.S.C.A. Section 351(c). If the quality of the device does fall below that which it purports or is represented to be, the product is deemed "adulterated" under the statute. The consequence of a product being adulterated is that it may not be marketed until and unless its adulterated quality is rectified.

12. There are two routes to the market for a medical device. One route, the pre-market approval application requires a full set of pre-clinical and clinical studies and is generally viewed as the most thorough device application process. A second route allows devices that are substantially equivalent to a marketed device ("the predicate") to submit a 510(k) application that establishes "substantial equivalence."

13. A manufacturer who submits a 510(k) application must assure that any device submitted under this 510(k) route be as safe and effective as its predicate device and not raise new questions about safety or effectiveness.

14. Bard IVC filter medical devices known as the Recovery and G2 were intended to be deployed in the inferior vena cava (IVC), to prevent pulmonary embolism in patients at risk for such outcomes, and for whom traditional anti-coagulation was contra-indicated. On July 10, 2002, Bard submitted an application to FDA for 510(k) clearance of the Recovery Filter (RNF), citing the Simon Nitinol Filter (SNF) System as one of the predicate devices. Accordingly, Bard was required to establish that the RNF was as safe and effective as the SNF.

15. [redacted]

16. [redacted]

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f. [redacted]

III. BARD MARKETED THE RECOVERY AND G2 IVC FILTERS UNDER THE 510(K) REGULATORY FRAMEWORK WHICH REQUIRED A SHOWING OF SUBSTANTIAL EQUIVALENCE TO PREDICATE DEVICES AND NOT PROOF OF SAFETY AND EFFICACY.

A. General Framework for the Regulation of Medical Devices.

20. The Food and Drug Administration (FDA) is one of the nation's most important consumer protection agencies. It is responsible for implementing the nation's food, drug, and medical device laws. "Before 1976, medical devices could be marketed without review by the U.S. Food and Drug Administration (FDA). Periodic attempts to regulate some devices as drugs, for which the agency did require premarketing clearance, proved to be cumbersome and inadequate. Spurred by the increased technological complexity of devices and mounting disclosures of shortcomings involving pacemakers, intrauterine devices, and intraocular lenses, Congress enacted the comprehensive Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act. The primary purpose of the amendments was to ensure that new devices were safe and effective before they were marketed." Kessler DA *et al.*, The Federal Regulation of Medical Devices, *The New England Journal of Medicine*, August 8, 1987.

21. The Federal Food, Drug, and Cosmetic Act (hereinafter, the "Act") (21 U.S.C. 301 *et seq.*), as amended by the Medical Device Amendments of 1976 (the "1976 amendments") (Public Law 94-295), the Safe Medical Devices Act of 1990 (the "SMDA") (Public Law 101¬629), the Food and Drug Administration Modernization Act of 1997 ("FDAMA") (Public

[2] This Overview is not intended as a comprehensive set of my opinions in this case. The full set of my opinions is set forth in the body of the Report, below.

Law 105-115), the Medical Device User Fee and Modernization Act ("MDUFA") (Public Law 107¬250) and the medical device provisions of the Food and Drug Administration Amendments Act of 2007 ("FDAAA") (Public Law 110-85), along with the applicable regulations in the Code of Federal Regulations, established a framework for the regulation of medical devices intended for human use.

22. Congress established three classes of devices, based on the regulatory requirements needed to provide reasonable assurance of their safety and effectiveness. The three classes of devices are class I, class II, and class III. Class I devices present no unreasonable risk of illness or injury and are subject to regulation through "general controls." 21 U.S.C. 360c(a)(1)(A). Class II devices are potentially more harmful and are subject to general controls, but FDA in addition has authority to require that such devices comply with other "special controls." 21 U.S.C. 360c(a)(1)(B). Class III devices present "a potential unreasonable risk of illness or injury." 21 U.S.C. 360c(a)(1)(C)(ii)(II).

23. In drafting the 1976 amendments, Congress divided medical devices in two different ways: (1) according to three classes noted above — class I, II, or III, and (2) according to seven basic categories — pre-amendment, post-amendment, substantially equivalent, implant, custom, investigational, and transitional. The current regulatory scheme involved weaving these two methods of subdivision into a workable statutory framework. Unlike the regulation of new drugs, in which standards of safety and effectiveness are applied uniformly, the regulation of devices is based primarily on risk.

24. More specifically, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as pre-amendments devices, are classified after FDA has: (1) received a recommendation from a device classification

panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device.[3]

25. Devices that were not in commercial distribution prior to May 28, 1976, generally referred to as post-amendments devices, are classified automatically by statute (section 513(f) of the Act (21 U.S.C. 360c(f)) into class III without any FDA rulemaking process. Those devices remain in class III and require a manufacturer to submit to FDA a premarket approval application, unless or until: (1) the device is reclassified into class I or II; (2) FDA issues an order classifying the device into class I or II in accordance with section 513(f)(2) of the Act (21 U.S.C. 360c(f)(2)); or (3) FDA issues an order finding the device to be substantially equivalent, under section 513(i) of the Act (21 U.S.C. 360c(i)), to a predicate device that does not require premarket approval.

26. Before a Class III device may be introduced into the market, a manufacturer must obtain a "premarket approval" ("PMA" may refer to either premarket approval or premarket application) from FDA. (21 U.S.C. 360c(a)(1)(C), 360e(a)). To obtain a PMA, the manufacturer must submit information to FDA in a premarket approval application that provides reasonable assurance that the device is safe and effective for its intended use. (21 U.S.C. 360c(a)(1)(C), 360e(a), (c), and (d) (1994 & Supp. IV 1998); 21 C.F.R. Pt. 814).

27. PMA is the most detailed type of device marketing application and review required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). PMA requires clinical testing to assure safety and effectiveness.

[3] Section 513 of the Act (21 U.S.C. 360c).

28. A "grandfathering" provision permits Class III devices that were on the market before the Medical Device Amendment's enactment to remain on the market until FDA initiates and completes a rulemaking requiring the submission of a PMA. (21 U.S.C. 360e(b)(1)(A)). Congress permitted manufacturers to distribute similar devices by showing through a premarket notification process that they are "substantially equivalent" to grandfathered devices. (21 U.S.C. 360e(b)(1)(B)). That premarket notification process is known as the "Section 510(k) process," referring to the applicable section of the Act (21 U.S.C. 360(k)). A device is "substantially equivalent" to a grandfathered device only if, *inter alia*, the device has the same "intended use" as the predicate device. (21 U.S.C. 360c(i)(1)(A) (1994 & Supp. IV 1998)).

29. In brief, the following summarizes how the statutory provisions operate in practice:

a. Medical devices are classified into one of three classes, I, II, or III.

b. Class III devices pose the greatest risk. Class I devices pose the least regulatory risk.

c. The class that a device is in determines the regulatory requirements.

d. Most class II devices can get on the market by what is called a premarket notification or 510(k) process.

e. A device that requires the submission of a premarket notification 510(k) cannot be commercially distributed until an authorizing letter of substantial equivalence ("clearance") from FDA is received by the manufacturer.

f. A 510(k) application must demonstrate that the device is substantially equivalent to a device that (1) was legally in commercial distribution in the US before May 28, 1976; or (2) has been determined by FDA to be

substantially equivalent. 510(k) premarket applications can "piggyback" by demonstrating substantial equivalence to a device that has been found substantially equivalent. This practice has led to significant controversy and concern that many important devices are not being reviewed for safety and effectiveness.[4]

g. Class III devices need to get on the market through the more thorough Premarket Approval Application process or PMA.

h. When it enacted the 1976 Medical Device Amendments, Congress required that all implanted devices (devices that were implanted in the human body) be categorized as Class III and thus subject to safety and efficacy review.

i. The PMA process is more involved and includes the submission of clinical data to support claims made for the device.

j. Devices that are being studied or evaluated are considered investigational devices. In order to obtain the clinical data to support a submission of a device, the manufacturer needs to submit an Investigational Device Exemption (IDE). Higher-risk investigational devices are classified as "significant risk" devices and require greater scrutiny.

k. An IDE allows the investigational device to be used in a clinical study to collect safety and effectiveness data required to support a PMA application or a premarket notification 510(k) submission to FDA.

l. Clinical studies of devices with significant risk must be approved by FDA and an Institutional Review Board ("IRB") before a study can begin.

[4] Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years (2011).

m. Studies of devices of non-significant risk must be approved by the IRB before a study can begin.

n. An IRB is a committee that has been formally designated to approve, monitor, and review research studies involving humans with the responsibility to protect the rights and welfare of the research subjects.

o. When a physician uses an investigational device, the protocols involving those investigational devices must be approved by a local IRB. A local IRB can be established by a university, hospital, or other institution. Each IRB must have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, to safeguard the rights and welfare of human subjects. (45 C.F.R. § 690.101).

p. The Center for Devices and Radiological Health within FDA is delegated, by the Commissioner, with the responsibility for regulating medical devices.

B. Substantial Equivalence.

30. According to FDA:

"A 510(k) requires demonstration of substantial equivalence to another legally U.S. marketed device. Substantial equivalence means that the new device is at least as safe and effective as the predicate.

A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate; **or**
- has the same intended use as the predicate; **and**
- has different technological characteristics and the information submitted to FDA:
    - does not raise new questions of safety and effectiveness; **and**

- demonstrates that the device is at least as safe and effective as the legally marketed device.

A claim of substantial equivalence does not mean the new and predicate devices should be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable."

[http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm, Emphasis in original]

31. FDA has also stated: "A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR 807.92(a)(3)) that is not subject to PMA. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims."[5]

32. Thus, to qualify for substantial equivalence, a device must not raise new questions about safety and effectiveness.

C. Substantial Equivalence is Not FDA Approval — It is Clearance.

33. A determination by the FDA in the 510(k) process that a device is substantially equivalent to a predicate device is not a finding that the device is safe and effective for its intended conditions of use.

34. The fact that a 510(k) clearance is not a finding of safety and efficacy was addressed by the United States Supreme Court in the *Medtronic v. Lohr* case.[6]

35. The United States government, through the Solicitor General, filed a brief in that case setting out the position of FDA and the United States government, which stated: "[t]he

[5] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm.
[6] *See Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996).

clearance of a post-Amendments device under Section 510(k)—based on a determination that the device is substantially equivalent to a pre-Amendments Class III device—does not reflect a determination by the FDA that the device is safe and effective, much less a specific determination that the device's design is required to ensure its safety and effectiveness. [A] determination of substantial equivalence...is not equivalent to an approval by the FDA of the device's safety and effectiveness.' H.R. Rep. No. 808 [101st Cong., 2d Sess. (1990)], at 14 . . . As the court of appeals observed, the FDA ordinarily will not have determined whether the pre-Amendments device was safe and effective (since the FDA lacked the general authority to do so prior to enactment of the Amendments)....[A]ccordingly, FDA regulations specify that a substantial equivalence determination 'does not in any way denote official approval of the device,' and that any representation conveying 'an impression of official approval...is misleading and constitutes misbranding."[7]

36. The Court, in its opinion, distinguished the "rigorous PMA review" from the 510(k) clearance process and found them "by no means comparable."[8]

37. The Court stated that "in contrast to the 1,200 hours necessary to complete a PMA review, the §510(k) review is completed in an average of only 20 hours."[9]

38. The Court specifically stated: "Although 'substantially equivalent' Class III devices may be marketed without the rigorous PMA review, such new devices, as well as all new Class I and Class II devices, are subject to the requirements of § 360(k). That section imposes a limited form of review on every manufacturer intending to market a new device by requiring it to submit a `premarket notification' to the FDA (the process is also known as a § 510(k) process,'

[7] Brief for the United States as Amicus Curiae Supporting Respondents/Cross-Petitioners, pp. 19-20, *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996) (No. 95-754).
[8] *Lohr*, 518 U.S. 470 at 478.
[9] *Id.*

after the number of the section in the original Act). If the FDA concludes on the basis of the § 510(k) notification that the device is 'substantially equivalent' to a pre-existing device, it can be marketed without further regulatory analysis (at least until the FDA initiates the PMA process for the underlying pre-1976 device to which the new device is 'substantially equivalent'). The § 510(k) notification process is by no means comparable to the PMA process; in contrast to the 1,200 hours necessary to complete a PMA review, the § 510(k) review is completed in an average of only 20 hours. *See* 1987 Hearings, at 384. As one commentator noted: 'The attraction of substantial equivalence to manufacturers is clear. [Section] 510(k) notification requires little information, rarely elicits a negative response from the FDA, and gets processed very quickly.' Adler, The 1976 Medical Device Amendments: A Step in the Right Direction Needs Another Step in the Right Direction, 43 Food Drug Cosm. L. J. 511, 516 (1988); *see also* Kahan, 39 Food Drug Cosm. L. J., at 514-519."[10]

39. The Court noted "[t]he 510(k) process is focused on *equivalence*, not safety." Specifically, the Court stated "[t]he company's defense exaggerates the importance of the §510(k) process and the FDA letter to the company regarding the pacemaker's substantial *equivalence* to a grandfathered device. As the court below noted, '[t]he 510(k) process is focused on equivalence, not safety.' 56 F. 3d, at 1348. As a result, 'substantial equivalence determinations provide little protection to the public. These determinations simply compare a post-1976 device to a pre-1976 device to ascertain whether the later device is no more dangerous and no less effective than the earlier device. If the earlier device poses a severe risk or is ineffective, then the later device may also be risky or ineffective.' Adler, 43 Food Drug Cosm. L.

[10] *Id.* at 478-479.

J., at 516. The design of the Model 4011, as with the design of pre-1976 and other `substantially equivalent' devices, has never been formally reviewed under the MDA for safety or efficacy."[11]

40. Justice O'Connor, with whom Chief Justice Scalia and Justice Thomas joined, concurring in part and dissenting in part, stated "[t]he § 510(k) process merely evaluates whether the Class III device at issue is substantially equivalent to a device that was on the market before 1976, the effective date of the MDA; if so, the later device may be also be marketed."[12]

41. One may argue that to the extent that there are no differences between a substantially equivalent device and its predicate, the device that is found to be substantially equivalent should be safe and effective. The problem with that argument is that the predicate device has never itself been found to be safe and effective.

42. There are instances where FDA can under the 510(k) clearance process request "clinical data." FDA can request clinical data from a manufacturer to determine whether a device's indication for use falls within the device's intended use. FDA can also request clinical data if the agency has determined that the 510(k) submission has new technological characteristics relative to its predicate. That determination of new technological characteristics is based in significant part on the manufacturer telling the FDA that the device has new technological characteristics.

43. FDA acknowledges the 510(k) process has "evolved" over time.[13] On July 28, 2014, FDA stated in a guidance document, "[t]he 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate) device) differs from the PMA review standard (reasonable assurance of safety and effectiveness). The 510(k) review standard

[11] *Id.* at 492-493 (emphasis in original).
[12] *Id.* at 513.
[13] The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] —Guidance for Industry and Food and Drug Administration Staff (July 28, 2014).

is comparative, whereas the PMA standard relies on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review. The standard for a determination of substantial equivalence in a 510(k) review is set out in section 513(i) of the FD&C Act. . . ." *Id.* at 6.

44. The Institute of Medicine in its report entitled "Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years" (hereinafter, "IOM Report"), concluded "The 510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices with some exceptions. The 510(k) process cannot be transformed into a premarket evaluation of safety and effectiveness as long as the standard for clearance is substantial equivalence to any previously cleared device." IOM Report, at p. 5.

45. FDA has limited resources and must rely on the data submitted by the manufacturer.

D. FDA Standards for Device Labelling

46. The general labeling requirements for medical devices are set out in 21 CFR 801.

47. On March 8, 1991, the Director of the Office of Device Evaluation made public a "Device Labeling Guidance." FDA, General Program Memorandum #G91-1 (http://www.fda.gov/RegulatoryInformation/Guidances/ucm081368.htm)

48. The document stated "[w]hile this guidance is primarily intended to ensure the adequacy of, and the consistency in, the labeling information for devices subject to premarket approval, it may also contribute to premarket notification reviews." Id.

49. The Device Labeling Guidance set out the following general sections for a device label: 1) Indications for Use, 2) Contraindications, 3) Warnings, 4) Precautions, and 5) Adverse Reactions.

50. The Device Labeling Guidance stated for the Warnings section in relevant part: "Describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. Include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the device. A causal relationship need not have been proved." Id.

51. In addition to these labeling requirements, Section 502(a) of the Federal Food, Drug & Cosmetic Act states that a device is misbranded if its labeling is false or misleading in any particular.

52. FDA guidance titled "Labeling: Regulatory Requirements for Medical Devices," dated August 1989, states:

> "Section 502(a) declares that a drug or device is misbranded if its labeling proves false or misleading in any particular. The phrase 'false or misleading' is not confined in meaning to untrue, forged, fraudulent, or deceptive. In fact, the word, statement, or illustration may be true in the strict sense of the word; however, the labeling can be deemed by the FDA to be in violation of the law if it proves deceptive to the customer. It is not a necessary condition that the labeling should be flatly and baldly false; the word 'misleading' in the Act means that labeling is deceptive if it is such as to create or lead to a false impression in the mind of the reader. A 'false impression' may result not only from a false or deceptive statement, but may also be instilled in the mind of the purchaser by ambiguity or misdirection. It may also be caused by failure to inform the consumer of facts that are relevant to those statements actually made. In other words, the label that remains silent as to certain consequences may be as deceptive as the label that contains extravagant claims."
>
> (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm095308.pdf, at p. 4)

53. FDA's labeling guidance also gives examples of false and misleading misrepresentations. These examples include: "ambiguity, half-truths, and trade puffery;" and "failure to reveal material facts, consequences that may result from use, or the existence of difference of opinion." Thus, labeling may be misbranded if it makes a misleading statement or

fails to inform the consumer of facts that are relevant to those statements actually made. (*Id.*, at 4-5).

54. A "Perspective" in The New England Journal of Medicine, June 1st, 2006, arose from the work of a panel that conducted an investigation of some potentially fatal malfunctions of implantable defibrillators. That commentary included certain principles relevant to the framework for conduct of medical device manufacturers, as follows:

a. "First, manufactured products can never be entirely free of design or manufacturing flaws, but when the consequence of a malfunction is a potentially fatal event, tolerance and surveillance strategies should aim to achieve a risk of malfunction that is as close to zero as possible.
b. Second, physicians must know about the performance features of any device they recommend for a patient so that they can carry out their ethical obligation of obtaining informed consent. This information must be in a form that is understandable and clinically useful.
c. And third, patients have a right to obtain product information so they can make informed decisions about risks and benefits and can understand what expectations are reasonable.
d. All companies are required by the Food and Drug Administration to evaluate device malfunctions systematically in the postmarketing phase to identify those that are clinically significant to correct defects and to act to prevent failures in performance. These internal processes necessarily center on engineering skills and methods, but the consequences of device malfunctions are more than an issue for engineering. They have clinical implications for patients that may include a risk of fatal events. Thus, engineering performance standards are insufficient benchmarks without evaluation by experts of the possible effects on individual patients.
e. [C]ompanies must reevaluate their approach to patient safety in the context of communication. A critical question is when and how information about product performance should be communicated to physicians and patients. Although the issues, both ethical and practical, are complex, one conclusion is clear: Transparency in matters that affect patient safety should be embraced as a primary corporate obligation.
f. From the perspective of physician and patient expectations, corporate responsibility and public perception, we believe that proactive communication policies centering on the proper use of active and passive transparency should be the norm.
g. Corporate culture fosters a loyalty to corporate goals that may create unintended bias and distorted perceptions about product performance and patient safety."

Robert J. Myerburg, M.D., David W. Feigal, Jr., M.D., M.P.H., and Bruce D. Lindsay, M.D. "Life-Threatening Malfunction of Implantable Cardiac Devices," *The New England Journal of Medicine*, 2006 Jun 1;354(22):2309-11.

E. Physicians' Abilities to Assess the Safety and Efficacy of Medical Devices.

55. In my opinion, physicians are rarely in a position to determine whether a device is safe and effective. That is the responsibility of the manufacturer.

56. Physicians in practice are rarely in a position to undertake scientific studies to assess the safety and efficacy of medical devices.

57. Physicians in practice are rarely in a position to undertake clinical studies to assess the safety and efficacy of medical devices.

58. There are physicians who are specially-trained and have dedicated their careers to investigating the safety and efficacy of medical devices. In many instances they undertake studies of medical devices at the behest of the manufacturer who intends to sell the device. In most cases, it is the manufacturer that funds physician investigators to undertake such clinical trials. These physician investigators are usually distinct from physicians in practice, whose primary focus is on taking care of patients.

59. Physicians in practice are in the position of reading the medical literature and keeping abreast of developments. Time constraints limit the ability of these physicians to keep abreast of all medical literature on a subject.

60. While physicians in practice read the medical literature, articles dealing with specialized scientific questions relating to a device are often published in the scientific, rather than medical, literature. It is more likely that a physician in practice will read the medical literature rather than the scientific literature. For example, engineering and other pre-clinical data could be published in the scientific engineering literature. Data that has clinical relevance to practicing physicians would likely be published in the medical literature.

61. The results of scientific and clinical testing done by a manufacturer are submitted as part of a 510(k) or PMA application. Those results, unless published elsewhere, are usually not available to practicing physicians. In certain instances, FDA may put online portions of a 510(k) application that were the subject of a Freedom of Information Act request. More generally, 510(k) listings and/or clearance letters, in contrast to the application itself, are available online. It would be the rare instance where a practicing physician would review the scientific and clinical testing that is part of a 510(k) or PMA application, unless such scientific and clinical testing was published elsewhere.

62. Physicians in practice gather their information about the safety and efficacy of a medical device from various sources. These may include the IFU, the medical literature, peers, teachers, conferences, promotional materials, and actual medical practice.

63. While a physician in practice can observe how a device performs in an individual or group of patients, such a physician cannot assess the safety and efficacy of a device in a controlled setting.

64. Observations of adverse events from a physician in practice, while anecdotal, are important pieces of information that comprise the "safety profile" of a device.

65. As FDA has long acknowledged, while isolated case reports, random experience, and reports lacking sufficient details to permit scientific evaluation are not regarded as valid scientific evidence to demonstrate safety or effectiveness, such information may be considered in identifying a device that has questionable safety and effectiveness.

IV. BARD HAD AN OBLIGATION TO ASSURE THAT THE RECOVERY FILTER WAS AT LEAST AS SAFE AND EFFECTIVE AS THE SIMON NITINOL FILTER.

66. Bard submitted a 510(k) application for its Recovery Nitinol Filter (RNF) on July 11, 2002 to the FDA. On November 27, 2002 the FDA cleared the device for market. See,

FDA510(k) Premarket Notification Database (visited 9/7/2016), http://www.accessdata.fda.gov. (BPV-17-01-00112441)

67. According to FDA: "a 510(k) requires demonstration of substantial equivalence to another legally U.S. marketed device. Substantial equivalence means that the new device is at least as safe and effective as the predicate." (See http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k, last accessed August 9, 2016)

68. According to Defendants' expert Dr. Donna B. Tillman, Bard had an obligation to assure that (a) "the device continues to be safe and effective and that they meet FDA's quality system requirements throughout the life of the device," (b) "[a]ssessed overall, the safety and effectiveness of the device could not be worse than the predicate device;" and (c) "[the device] needs to be as safe and effective as the predicate device." (Deposition of Dr. Donna B. Tillman, 06/12/2014, 101:20-23; 116:1-3 and 120:6-7)

69. As noted by FDA reviewers, "IVC filters are class II devices regulated with special controls requiring FDA clearance of a 510(k) premarket notification, which demonstrates that the device under review is as safe and effective as a device already on the market." (BPVEFILTER-01-00336554-558 at 557)

70. Bard cited the Simon Nitinol Filter/Straight Line System ("SNF") and the Titanium Greenfield Filter ("Greenfield") as the predicate devices. (BPV-FULLER-00001375-379 at 375) (*See*, Deposition testimony of Gin Schultz, 81-82:18-24)

71. In my opinion, Bard had an obligation to assure that the Recovery Filter was at least as safe and effective as the Simon Nitinol Filter.

V. BEFORE AND AFTER PRODUCT MARKETING, BARD FAILED TO ASSURE THE SAFETY OF THE RECOVERY AND MODIFIED RECOVERY (G2) FILTERS AND FAILED TO REASONABLY RESPOND TO EVIDENCE OF SAFETY CONCERNS.

A. Prior to Marketing of the Recovery Filter

72. On November 1, 1999, Nitinol Medical Technologies submitted a 510(k) application for a modified Simon Nitinol filter and delivery system known as the Recovery Filter System. (BPVE-01-01059026-153 at 036)

73. On December 10, 1999, FDA requested additional information to support the proposed modifications, including the need for clinical data. (BPV-17-01-00051625-626 at 625)[14]

74. On October 19, 2001, Bard acquired all rights and responsibilities for the Recovery Nitinol Filter (RNF) from Nitinol Medical Technologies (NMT). [15] (BPVEFILTER-01-00003802-836 at 804)

75. On July 10, 2002, Bard submitted a special 510(K) application (K022236) for changes to the Simon Nitinol Filter System for a device that would be known as the Recovery Filter (RNF).[16,17] Subsequent to the submission of the application to the FDA, FDA requested additional information that Bard then submitted.[18,19] (BPV-17-01-00057926 – 930)

14 [redacted]

15 [redacted]

17 [redacted]

76. On November 27, 2002, Bard received a substantially equivalent letter from FDA that stated that the device labeling and any promotional materials include a specific statement that the safety and effectiveness of the device for use as a retrievable or temporary filter had not been established.[20] (BPV-TRIAL-EXHIBIT-1245_0001-0003)

77. On December 20, 2002, the RNF product was launched[21] in the United States. (BPVEFILTER-01-00003802-836 at 804)

1. [redacted]

78. [redacted]

[redacted]

19 [redacted]

20 [redacted]

21 [redacted]

[redacted]

98. [redacted]

[redacted]

99. [redacted]

[redacted]

100. In my opinion, when new and continuing questions about safety and effectiveness are raised, the new device cannot be substantially equivalent to predicate devices.[29]

[redacted]

[27] [redacted]

[28] [redacted]

[29] [redacted]

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[redacted]

276. [redacted]

3. [redacted]

a. Bard's use of reporting rates

277. Bard had an opportunity to undertake clinical trials that compared its Recovery device to its predicate, the SNF. Bard did undertake to have a clinical series done for the Recovery device by Dr. Murray Asch, as noted above, that would assess the retrievability of the Recovery Filter; but that study had no comparator or control, and did not assess the safety and

efficacy of the Recovery Filter as a permanent device. [redacted]

278. [redacted]

279. [redacted]

280. [redacted]

281. [redacted]

282. [redacted]

283. [redacted]

1. [redacted]

2. [redacted]

284. In my experience, there is a greater chance of knowing about adverse events when the adverse event is clearly associated with the device and the event is of major clinical significance such as death.

285. In many instances, the limitations of exposure data result from the need to utilize estimates of sales data from third party vendors. [redacted]

286. Moreover, comparing reporting rates of two devices sold by the same company as in the case of both the SNF and the Recovery Filter where Bard marketed both devices (for the SNF, K944353, clearance on April 28, 1995, and from inception for the Recovery Filter, cleared for marketing on November 27, 2002) eliminates some of the variability when comparing devices from different manufactures with different surveillance practices, terminologies, and reporting practices. [redacted]

287. In my opinion, in most instances, when making risk determinations, it is of value to have evidence from multiple sources. In this instance, as noted above, evidence from preclinical testing needs to be viewed in conjunction with adverse event reporting rates.

b. Differences in adverse event reporting rates can be valuable across similar products, have served as a necessary and sufficient basis for product withdrawal, and are particularly useful where such rates are accompanied by consistent, supportive evidence from pre-clinical bench testing.

288. Despite the known limitations of adverse event data, FDA officials have stated, "Spontaneous AE/ADR reports have at times served as a necessary and sufficient basis for regulatory actions including product withdrawals. For instance, in August 2001 the manufacturer of cerivastatin [Baycol] withdrew that drug from marketing based on 'a markedly increased reporting rate of fatal rhabdomyolysis' compared to the other drugs in the statin class.[Citation omitted.] Additional confirmation of the unacceptably high risk of rhabdomyolysis with cerivastatin was eventually available 3 years later when results of a well-designed epidemiologic study were published. Clearly, that time frame would have been too long to delay decisive action, which in retrospect was soundly based on the) signal from spontaneous reports."[57] (Dal Pan, et al., in Strom, *Pharmacoepidemiology,* 5th ed. 2012, Chapter 10, pp. 137-157, at 139-40.

289. FDA officials published their reporting rate analysis, which showed that the rate of fatal rhabdomyolysis with Baycol was 16-80 times higher than with the other statins. Staffa, et al; *New England Journal of Medicine* 2002; 346:539-540. Staffa and colleagues at FDA reported that they determined reporting rates for the various statin drugs with numerators derived from spontaneous adverse event reports and denominators consisting of IMS data on prescriptions sold. (Dal Pan, et al., in Strom, *Pharmacoepidemiology,* 5th ed. 2012, Chapter 10, pp. 137-157, at 139-40.)

290. In the March 2005 "Guidance for Industry – Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," the FDA's Center for Drug Evaluation and Research

[57] *See* Feigal deposition testimony see Schedule.

(CDER) discussed the limitations of adverse event reporting systems, including "under-reporting" of event numerators, and uncertain denominators. However, the Guidance stated:

> "Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure in the denominator. FDA recommends that whenever possible, the number of patients or person time exposed to the product nationwide be the estimated denominator for a reporting rate. FDA suggests that other surrogates for exposure, such as numbers of prescriptions or kilograms of product sold, only be used when patient-level estimates are unavailable. FDA recommends that sponsors submit a detailed explanation of the rationale for the selection of a denominator and a method of estimation.
>
> *Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products* or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered as exploratory or hypothesis-generating. Reporting rates can by no means be considered incidence rates, for either absolute or comparative purposes."
>
> (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf, last accessed on August 28, 2016, emphasis added, references omitted)

291. As noted in FDA's March 2005 Guidance, FDA recommends that sponsors "submit a detailed explanation" for their adverse event reporting rates calculations.

292. FDA's March 2005 Guidance does not address the role or importance of adverse event reporting rates when they are accompanied by supportive, consistent information from other sources.

293. [redacted]

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d. Statistical analysis of adverse events of Recovery Filter compared to SNF

307. As has been my past practice, although I am a Professor of Biostatistics, I have repeatedly throughout my career asked other biostatisticians to carry out statistical analyses of data.

308. For this report, I asked counsel to engage a biostatistician to review Bard's adverse event reporting analyses concerning the Recovery and Modified Recovery Filters, including performing the type of analyses that Bard carried out at various points in time. Dr. Rebecca Betensky is a Professor of Biostatistics at the Harvard School of Public Health. While I did not know Dr. Betensky prior to her engagement, a review of her resume indicates that she is a well-qualified senior biostatistician.

309. I received and reviewed a copy of Dr. Betensky's expert report which is attached as a Schedule.

310. Specifically, Dr. Betensky found that there were statistically significant increased reporting risk ratios[62] that provide evidence of increased risk of the Recovery Filter compared to SNF and other competitive filters. This is particularly important in light of her findings of statistically significant poorer performance of the Recovery filter in preclinical migration resistance testing.

311. [redacted]

[62] I am aware that the term "reporting rate ratio" is sometimes used to express the same concept. (*See, e.g.*, Pierfitte, *et al.*, "Is reporting rate a good predictor of risks associated with drugs?" *Br. J. Clin. Pharmacol.* 1999; 47:329-331)

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[redacted]

(September 5, 2016 Expert Report of Dr. Rebecca Betenksy, p. 13-14)

314. In my opinion, according to the analysis done by Dr. Betensky, with which I am in agreement, taking into account the strengths and limitations of the methodology used, and in light of the preclinical testing results, there was evidence of a statically significant increase of filter embolization deaths, migration, perforation, filter fractures, detached components, and tilted filters [redacted]

4. [redacted]

315. [redacted]

63 [redacted]

PAGES 115 – 179 REDACTED IN THEIR ENTIRETY

464. [redacted]

465. [redacted]

VI. [redacted]

A. [redacted]

466. [redacted]

467. [redacted]

468. [redacted]

469. [redacted]

470. [redacted] as referenced in the SIR "Quality Improvement Guidelines," initially published in 2001 and republished in 2003, with Grassi as lead author (Grassi, *et al.*, "Quality Improvement Guidelines for Percutaneous Permanent Inferior Vena Cava Filter Placement for the Prevention of Pulmonary Embolism" *J Vasc Interv*

Radiol 2003; 14:S271-S275, hereinafter, the "SIR Guidelines").

471. None of the references in the SIR Guidelines article provided any information concerning adverse events associated with the predicate SNF 1995 device, #K944353, for the relevant outcomes of Death, Filter Embolization, IVC Penetration, Migration, or Filter Fracture.[77]

472. For the outcome of "Death," the SIR Guidelines cited a single review article in support of a "Reported Rate" of 0.12% and a "Threshold" of "<1%." That article, reference #7 (Becker, *Arch Intern Med* 1992; 152:1985-94), was written before 1995, and it therefore provided no information relevant to Bard's obligation of substantially equivalent safety to the predicate SNF device.[78]

473. The SIR Guidelines listed the complication of "Filter Embolization," providing "Reported rates" of 2-5%, and a "Threshold" of 2%, citing 12 articles published between 1980 and 1993 (references 17, 24, 28-37). These articles necessarily have no information concerning the 1995 SNF predicate device that was not in use until after they were published.

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[77] For the outcome of "Access Site Thrombosis-Major," a single SIR reference published in 1999 may include limited information concerning the predicate SNF, although it is not possible to tell from the text. See, Blebea, et al., *J Vasc Surg* 1999; 30:821-829, which reported on access site thrombosis among patients between 1993-1998, a period that includes both the 1995 predicate SNF and its non-predicate predecessors. There were 11 patients with SNF devices among the 35 studied by the authors, and 7 of those had access site thrombosis; no information was provided as to which patients received pre-1995 or post 1995 devices, nor which devices were in place among the patients who experienced access site thrombosis. Bard compared adverse event reporting rates comparisons of the Recovery Filter to SIR reported rates for other outcomes, such as fracture, migration, and death, and not for access site thrombosis. See Schedule.

[78] In fact, the Becker article derived the rate of 0.12% from 3 deaths among 2,557 patients described in 24 studies: "These deaths involved misplacement of a Greenfield filter during insertion, hypotension and cardiac arrest minutes after insertion of a Gr